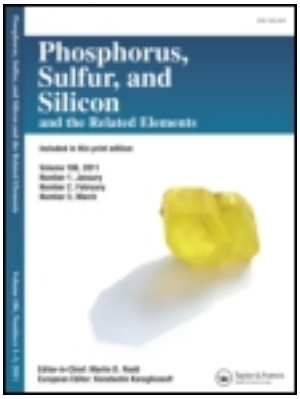

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Phase-Transfer Catalyzed Alkylation and Cycloalkylation of 2-Mercaptoquinazolin-4(3H)-One

A. Kh. Khalil [a]

[a] Chemistry Department, Ain Shams University, Abbasia, Cairo, Egypt

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Phase-Transfer Catalyzed Alkylation and Cycloalkylation of 2-Mercaptoquinazolin-4(3H)-One

A. Kh. Khalil
Chemistry Department, Ain Shams University, Abbasia, Cairo, Egypt

Solid/liquid phase-transfer catalyzed alkylation of 2-mercaptoquinazolin-4(3H)-one at 25°C by different organohalogen compounds in the presence of tetrabutylammonium bromide as a catalyst underwent, exclusively, S-monoalkylation or S- and N-, di-, or cycloalkylation, depending on the nature of alkylating agents.

Keywords Alkylation; cycloalkylation; mercaptoquinazolinone; phase-transfer catalysis

INTRODUCTION

Phase-transfer catalysis (PTC) is one of the promising methods in organic synthesis of specialty chemicals. In the last 20 years, a steadily increasing number of published papers and patents dealing with PTC topics and their applications. PTC is not merely important for substitutional reactions but, now a days, it is being applied extensively in polymer chemistry, heterocyclic chemistry, organometallic

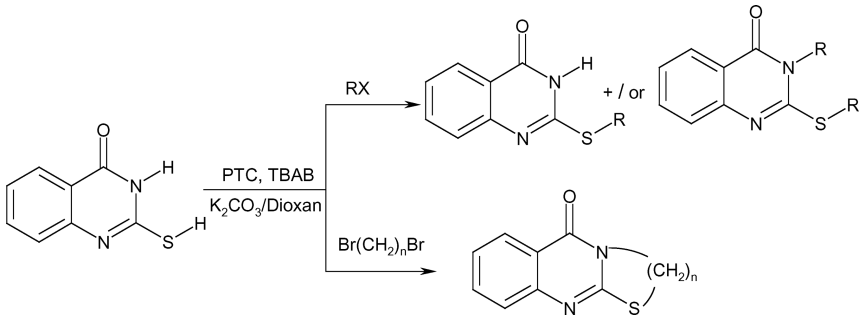

FIGURE 1

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Address correspondence to A. Kh. Khalil, Ain Shams University, Chemistry Department, Faculty of Science, Abbasia, Cairo, Egypt. E-mail: khalilali123@yahoo.com

synthesis, agrochemicals, dyes, flavors, perfumes, and pharmaceutical manufacturing.[1–3]

The technique of PTC has been applied extensively in the organic synthesis via substitution, displacement, condensation, elimination, Ylide-mediated reactions, redox, and polymerization. The biggest advantages of using the PTC technique to synthesize organic chemicals are the enhancing the reaction rate, carrying out the reaction at moderate conditions, and obtaining high selectivity of the main product with a high conversion of the reactants.[4,5]

On the other hand, 4(3H)-quinazolinones are the most frequently encountered heterocycles in medicinal chemistry with wide applications including anticonvulsant,[6] antihypertensive,[7] antidiabetic,[8] antibacterial,[9] antitumor,[10] antihistaminic,[11] and antiinflammatory[12] activities. Recent investigations on the biological activity of heterocycles containing a benzimidazole ring clearly show that they play an important role as selective neuropeptide YY1 receptor antagonists,[13] factor Xa inhibitors,[14] 5-lipoxygenase inhibitors for use as novel antiallergic agents,[15] poly polymerase inhibitors,[16] and as human cytomegalovirus inhibitors.[17]

RESULTS AND DISCUSSION

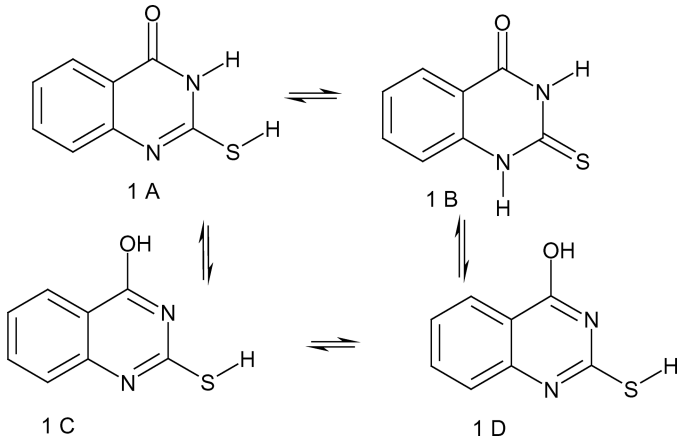
The approach reported here is an extension and continuation of my interest in alkylation of some heterocycles uender PTC conditions.[18–20] This work is aiming to study the reactivity of S-versus N-alkylation of 2-mercaptoquinazolin-4(3H)-one (**1**) via solid/liquid PTC conditions by some mono- and dihologen organic reagents as an efficient recent alkylation technique. Also, it is expected that the alkylated products might have biological and medicinal activities in analogy to the well known biologically active quinazolin-4(3H)-one derivatives.

2-mercaptoquinazolin-4(3H)-one (**1**) is existed, predomenantly, in four toutomeric forms (Scheme 1A–D).

The position of alkylation depends on the relative acidity and nucleophilicity of SH, NH, and OH.

The acidity of NH at the 3-position of structure **1B** of Scheme 1 is higher than at the 1-position, so N3 alkylation has a higher periority than N1.

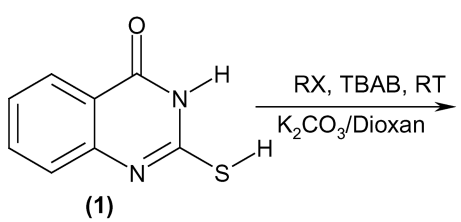
Spectral data and some reported articles[19–23] proved that 2-mercaptopyrimidinones existed, predomenantely, as 2-mercaptolactames such as **1A**. It is expected that monoalkylation occurs exclusively at S- rather than N-due to the higher ─SH acididty than ─NH, while dialkylation occurs at S- and N3 to give the dialkylated product.



SCHEME 1

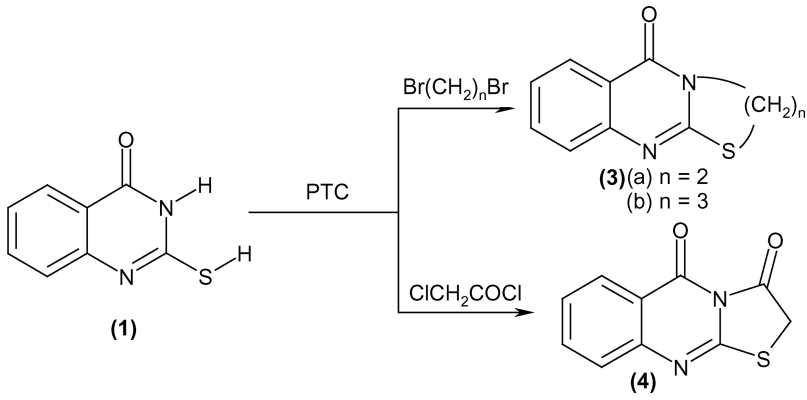
The optimized reaction conditions of PTC alkylation are the treatment of 2-mercaptoquinazolin-4(3H)-one (**1**) with haloorganic reagents in dioxane/anhydrous potasstium carbonate as liquid/solid phases in the presence of tetrabutylammonium bromide (TBAB) as catalyst with efficient stirring for 2–4 h at 25°C.

Treatment of 2-mercaptoquinazolin-4(3H)-one (**1**) with ethyl bromide, allyl bromide, bromoactylacetone, and diethyl bromomalonate in



(a) R = C_2H_5; R' = H
(b) R = CH_2-CH=CH_2; R' = H
(c) R = $CH(COCH_3)_2$; R' = H
(d) R = $CH(CO_2C_2H_5)_2$; R' = H
(e) R = R' = CH_3
(f) R = R' = C_6H_5-CH_2
(g) R = R'= $CH_2COC_6H_4OCH_3$-4
(h) R = R' = $CH_2CO_2C_2H_5$
(i) R = R' = $ClCH_2CO$

SCHEME 2



SCHEME 3

a 1:3 molar ratio, respectively, under the optimized PTC reaction conditions afforded, exclusively, S-monoalkylation to give **2a–d**, while with methyl iodide, benzyl bromide, ω-bromo-4-methoxyacetophenone, ethyl bromoacetate, and chloroacetyl chloride simultaneously underwent S- and N-dialkylation to give **2e–i**, respectively (Scheme 2).

On the other hand, under the same optimized PTC conditions, treatment of an equimolar amount of 2-mercaptoquinazolin-4(3H)-one (**1**) and dihalogen organic reagents such as 1,2-dibromoethane, 1,3-dibromopropane and chloroacetyl chloride underwent S- and N-cycloalkylation to give 2,3-dihydro-5H-[1,3]thiazolo[2,3-b]quinazolin-5-one (**3a**), 3,4-dihydro -2H, 6H-[1,3]thiazino[2,3-b]quinazolin-6-one (**3b**), and 5H-[1,3]-thiazolo-[2,3-b]quinazolin-3,5(2H)-dione (**4**), respectively (Scheme 3).

CONCLUSION

The feasibility study in this work revealed that PTC alkylation of mercaptoquinazolin-4(3H)-one (**1**) proceeds smoothly with a moderate yield (60–85%) and occurs in all cases, predominantly, at S- with monohalogen compounds, while simultaneously with S- and N-dialkylations of some cases. Also, PTC cycloalkylations was afforded, with dihalogen, organic reagents to give annulated heterocyclic systems such as thiazoloquinolinone and thiazinoquinolinone derivatives.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer's Spectrum RXIFT-IR spectrophotometer (ν in cm^{-1}). The NMR

spectra were recorded on a Bruker Avance DPX400 spectrometer, using TMS as internal standard (chemical shifts in δ values in ppm). Elemental analyses were preformed using a Perkine Elmer 2400, Series II micro analyzer. The key starting, 2-mercaptoquinazolin-4(3H)-one (**1**) is an Aldrich product and was used without further purification.

General Procedure

To a solution of 2-mercaptoquinazolin-4(3H)-one (1.78 g, 0.01 mol) (**1**) in dioxane (50 mL), anhydrous K_2CO_3 (2.7 g, 0.02 mol) and TBAB (0.9 g, 0.003 mol); the monohalogen organic reagents (0.03 mol) such as ethyl bromide, allyl bromide, bromoacetylacetone, diethyl bromomalonate, methyl iodide, benzyl bromide, ω-bromo-4-methoxyacetophenone, ethyl bromoacetate; and chloroacetyl chloride or a dihalgen organic reagent (0.01 mol) such as 1,2-dibromoethane, 1,3-dibromopropane, and chloroacetyl chloride was added. The reaction mixture was stirred vigorously at 25°C and monitored by TLC over the reaction period. After completion of the reaction, the dioxane was separated by filtration and the solvent was evaporated; then the residue was triturated with pet. ether 60–80°C to release the excess of the unreacted halogen reagent; then the residue was crystallized from the suitable solvent to give the product **2–4**. The K_2CO_3 residue was dissolved in water (50 mL) and acidified by hydrochloric acid (15% solution) to confirm if an acidic byproduct existed. In all cases, there is no byproduct isolated from K_2CO_3 residue.

2-Mercaptoquinazolin-4(3H)-one (1)

^{1}H NMR: δ (DMSO), 7.27 (t, 1H, Ph-H), 7.39 (d, 1H, Ph-H), 7.63 (t, 1H, Ph-H), 8.02 (d, 1H, Ph-H), 11.97 (s, 1H, NH), 12.56 (s, 1H, SH); ^{13}C NMR: δ (DMSO), 116.00 (C), 126.03 (CH), 127.12 (CH), 134.7 (CH), 135.73 (CH), 140.46 (C), 159.99 (C_2), 174.35 (C_4).

2-(Ethylthio)quinazolin-4(3H)-one (2a)

White crystals from ethanol; $C_{10}H_{10}N_2OS$ (206.71), Calcd.: C, 58.23; H, 4.89; N, 13.5; found: C, 58.55; H, 4.82; N, 12.99; yield 64%; m.p. 147°C; IR (KBr), 1580, 1678, 2878, 3318; ^{1}H NMR, δ ($CDCl_3$), 1.47 (t, 3H, CH_3), 3.32 (q, 2H, S-CH_2), 7.40, 7.61, 7.72, 8.26 (4H, Ar-H), 10.90 (s, 1H, NH); ^{13}C NMR, δ ($CDCl_3$), 14.44 (CH_3), 25.25 (CH_2), 119.87 (C), 125.73 (CH), 126.39 (CH), 126.60 (CH), 134.83 (CH), 149.21 (C), 154.54 (C_2), 163.03 (C_4).

2-(Allylthio)quinazolin-4(3H)-one (2b)

White crystals from pet. ether 60–80°C; $C_{11}H_{10}N_2OS$ (218.28), Calcd.: C, 60.53; H, 4.62; N, 12.83; found: C, 60.47; H, 4.58; N, 12.77;

yield 58%; m.p. 154°C; IR (KBr), 1581, 1668, 2871, 3310; ^{1}H NMR, δ ($CDCl_3$), 4.41 (d, 2H, C<u>H</u>$_2$), 5.62 (d, 1H, =C<u>H</u>$_b$), 5.82 (d, 1H, =C<u>H</u>$_a$), 6.45 (m, 1H, −C<u>H</u>=), 7.83, 8.03, 8.16, 8.67 (4H, Ar-<u>H</u>), 11.90 (s, 1H, N<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 33.32 (CH_2), 118.73 (=CH_2), 120.26 (C), 124.92 (CH), 125.73 (CH), 127.55 (CH), 133.87 (CH), 135.47 (CH), 149.01 (C), 154.24 (C_2), 163.03 (C_4).

3-[(4-Oxo-3,4-dihydroquinazolin-2-yl)thio]pentane-2,4-dione (2c)

Orange crystals from ethanol; $C_{13}H_{12}N_2O_3S$ (276.32), Calcd.: C, 56.51, H, 4.38, N, 10.14; found: C, 56.46; H, 4.33; N, 10.06; yield 62%; m.p. 208°C; IR (KBr), 1584, 1671, 2868, 3011; ^{1}H NMR, δ ($CDCl_3$), 2.35 (s, 6H, 2xC<u>H</u>$_3$), 4.11 (s, 1H, C<u>H</u>), 7.41–8.24 (4H, Ar-<u>H</u>), 12.53 (s, 1H, N<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 26.94 (CH_3), 64.67 (CH), 121.67 (C), 126.34 (CH), 127.18 (CH), 134.79 (CH), 147.27 (C), 154.88 (C_2), 162.07 (C_4), 197.13 (C=O).

Diethyl[(4-Oxo-3,4-dihydroquinazolin-2-yl)thio]malonate (2d)

Pale yellow crystals from ethanol; $C_{15}H_{16}N_2O_5S$ (336.37), Calcd.: C, 53.56; H, 4.75; N, 8.33; found: C, 53.66; H, 4.65; N, 8.41; yield 66%; m.p. 126°C; IR (KBr), 1658, 1747, 2881, 2982, 3321; ^{1}H NMR, δ ($CDCl_3$), 1.31 (txt, 6H, 2xC<u>H</u>$_3$), 4.24 (qxq, 4H, 2xOC<u>H</u>$_2$), 5.62 (s, 1H, C<u>H</u>), 7.36–8.22 (4H, Ar-<u>H</u>), 12.07 (s, 1H, N<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 51.82 (CH_3), 60.61 (CH), 62.94 (CH_2), 119.81 (C), 126.28 (CH), 126.80 (CH), 135.23 (CH), 148.57 (C), 152.73 (C_2), 163.39 (C_4), 165.60 (C=O).

3-Methyl-2-(methylthio)quinazolin-4(3<u>H</u>)-one (2e)

White crystals from pet. ether 40–60°C; $C_{10}H_{10}N_2OS$ (206.27), Calcd.: C, 58.23; H, 4.89; N, 13.58; found: C, 58.65; H, 4.82; N, 13.69; yield 85%; m.p. 66–68°C; IR (KBr), 1556, 1667, 2934; ^{1}H NMR, δ ($CDCl_3$), 2.65 (s, 3H, S−C<u>H</u>$_3$), 3.60 (s, 3H, N−C<u>H</u>$_3$), 7.35, 7.52, 7.65, 8.19 (4H, Ar-<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 14.45 (S−CH_3), 30.84 (N−CH_3), 118.89 (C), 124.65 (CH), 126.27 (CH), 127.65 (CH), 134.86 (CH), 147.39 (C), 157.48 (C_2), 161.81 (C_4).

3-Benzyl-2-(bezylthio)quinazolin-4(3<u>H</u>)-one (2f)

White crystals from pet. ether 60–80°C; $C_{22}H_{18}N_2OS$ (358.47), Calcd.: C, 73.72; H, 5.06; N, 7.81; found: C, 73.68; H, 5.12; N, 7.89; yield 73%; m.p. 95–97°C; IR (KBr), 1565, 1691, 2938, 3032; ^{1}H NMR, δ ($CDCl_3$), 4.50 (s, 2H, S−C<u>H</u>$_2$), 5.35 (s, 2H, N−C<u>H</u>$_2$), 7.23 (m, 10H, 2xC_6H_5), 7.40, 7.57, 7.65, 8.22 (4H, Ar-<u>H</u>); ^{13}C NMR, δ ($CDCl_3$), 37.24 (S−CH_2), 47.77 (N−CH_2), 119.67 (C), 126.48 (CH), 127.88 (CH), 129.06

(CH), 129.80 (CH), 134.93 (CH), 135.94 (C), 136.79 (C), 147.85 (C), 156.84 (C_2), 162.45 (C_4).

3-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}quinazolin-4(3H)-one (2g)

White crystals from ethanol; $C_{26}H_{22}N_2O_5S$ (474.54), Calcd.: C, 65.81; H, 4.67; N, 5.90; found: C, 65.92; H, 4.59; N, 6.01; yield 54%; m. p. 169°C; IR (KBr), 1597, 1680, 2909; ^{1}H NMR, δ ($CDCl_3$), 3.85 (s, 3H, O-C$\underline{H}_3$), 3.97 (s, 3H, O–C$\underline{H}_3$), 4.97 (s, 2H, S–C$\underline{H}_2$), 5.72 (s, 2H, N–C$\underline{H}_2$), 7.23–8.25 (12H, Ar-$\underline{H}$); ^{13}C NMR, δ ($CDCl_3$), 39.63 (S-CH_2), 49.70 (N–CH_2), 55.55 (OCH_3), 114.72 (CH), 115.19 (CH), 120.02 (C), 126.45 (CH), 127.63 (CH), 129.37 (C), 130.32 (CH), 134.68 (CH), 146.28 (C), 155.48 (C_2), 159.23 (C_4), 164.12 (C), 164.52 (C), 186.38 (C=O), 190.93 (C=O).

Ethyl{[3-(2-ethoxy-2-oxoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl]thio}acetate (2h)

White crystals from ethanol; $C_{16}H_{18}N_2O_5S$ (350.40), Calcd.: C, 54.85; H, 5.18; N, 7.99; found: C, 54.69; H, 5.19; N, 8.05; yield 75%; m.p. 249°C; IR (KBr), 1557, 1680, 1741, 2927, 2983; ^{1}H NMR, δ ($CDCl_3$), 1.34 (txt, 6H, 2xC$\underline{H}_3$), 4.11 (s, 2H, S–C$\underline{H}_2$), 4.32 (qxq, 4H, 2xO–C$\underline{H}_2$), 4.98 (s, 2H, N–C$\underline{H}_2$), 7.45, 7.57, 7.76, 8.25, (4H, Ar-$\underline{H}$); ^{13}C NMR, δ ($CDCl_3$), 14.08 (CH_3), 14.18 (CH_3), 34.63 (S–CH_2), 44.98 (N–CH_2), 61.96(OCH_2), 62.09 (OCH_2), 118.99 (C), 126.15 (CH), 127.12 (CH), 134.67 (CH), 147.13 (C), 154.38 (C_2), 161.36 (C_4), 166.76 (C=O), 168.19 (C=O).

S-[3-(Chloroacetyl)-4-oxo-3,4-dihydroquinazolin-2-yl]chloroethanethioate (2i)

White crystals from ethanol; $C_{12}H_8Cl_2N_2O_3S$ (331.18), Calcd.: C, 43.52; H, 2.43; N, 8.46; found: C, 43.66; H, 2.55; N, 8.41; yield 78%; m.p. 215°C; IR (KBr), 1572, 1701, 3074; ^{1}H NMR, δ ($CDCl_3$), 2.57 (s, 2H, NCOC$\underline{H}_2$), 3.20 (s, 2H, SCOC$\underline{H}_2$), 7.43, 7.60, 7.78, 8.29, (4H, Ar-$\underline{H}$); ^{13}C NMR, δ ($CDCl_3$), 43.98 (NCO$\underline{C}H_2$), 46.12 (SCO$\underline{C}H_2$), 118.67 (C), 125.13 (CH), 127.96 (CH), 128.77 (CH), 148.75 (C), 157.90 (C_2), 158.67 (C_4), 164.34 (NCO), 191.58 (SCO).

2,3-Dihydro-5H-[1,3]thiazolo[2,3-b]quinazolin-5-one (3a)

White crystals from pet. ether 60–80°C; $C_{10}H_8N_2OS$ (204.25), Calcd.: C, 58.81; H, 3.95; N, 13.72; found: C, 58.76, H, 4.09, N, 13.91; yield 63%; m.p. 63–65°C; IR (KBr), 1566, 1626, 1690, 3075; ^{1}H NMR, δ ($CDCl_3$), 3.45 (txt, 2H, S–C$\underline{H}_2$), 4.43 (txt, 2H, N–C$\underline{H}_2$), 7.24, 7.38, 7.54, 8.01, (4H, Ar-$\underline{H}$); ^{13}C NMR, δ ($CDCl_3$), 26.32 (S–$\underline{C}H_2$), 48.57 (N–$\underline{C}H_2$), 119.97 (C), 126.23 (CH), 127.39 (CH), 127.88 (CH), 134.75 (CH), 149.13 (C), 159.62 (C), 161.14 (C=O).

3,4-Dihydro-2H, 6H-[1,3]thiazino[2,3-b]quinazolin-5-one (3b)

White crystals from pet. ether 60–80°C; $C_{11}H_{10}N_2OS$ (218.28), Calcd.: C, 60.53; H, 4.62; N, 12.83; found: C, 60.59; H, 4.65; N, 12.89; yield 83%; m.p. 90–92°C; IR (KBr), 1607, 1676, 2934; ^{1}H NMR, δ ($CDCl_3$), 2.33(m, 2H, CH_2), 3.23 (t, 2H, S—CH_2), 4.21 (t, 2H, N—CH_2), 7.36, 7.51, 7.69, 8.18 (4H, Ar-H); ^{13}C NMR, δ ($CDCl_3$), 23.14 (CH_2), 27.91 (S—CH_2), 41.73 (N—CH_2), 119.38 (C), 125.63 (CH), 125.74 (CH), 126.92 (CH), 134.61 (CH), 147.34 (C), 153.94 (C), 161.48 (C=O).

5H-[1,3]Thiazolo[2,3-b]quinazolin-3,5(2H)-dione (4)

Yellow crystals from ethanol; $C_{10}H_6N_2O_2S$ (218.24), Calcd.: C, 55.04, H, 2.77, N, 12.84; found: C, 55.14; H, 2.66; N, 12.92; yield 51%; m.p. 251°C (dec.); IR (KBr), 1581, 1683, 1692, 2971; ^{1}H NMR, δ (Aceton-d_6), 4.11(s, 2H, CH_2), 7.42–8.13 (4H, Ar-H); ^{13}C NMR, δ ($CDCl_3$), 34.64 (CH_2), 121.73 (C), 125.12 (CH), 127.87 (CH), 135.23 (CH), 147.29 (C), 159.41 (C), 161.54 (C), 170.74 (C=O).

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